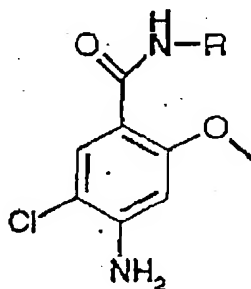


CLAIMS

1. Use of one or more compounds having agonist activity to a 5-HT<sub>4</sub> receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising the following 5-HT<sub>4</sub> receptor agonists: benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopramide, with the structural formula:



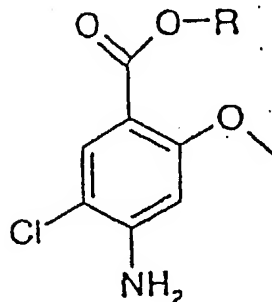
having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

AMENDED SHEET

AMENDED SHEET

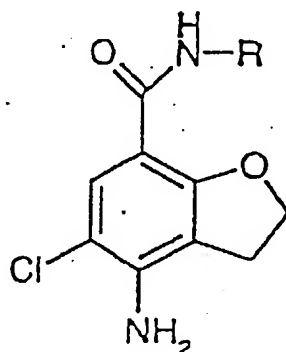
34

benzoic acid esters:

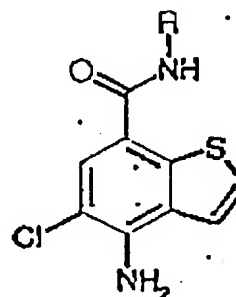
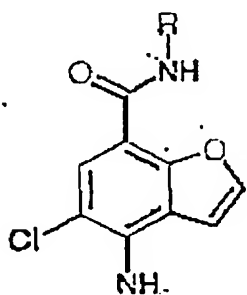


preferably ML 10302, RS 57639, and SR 59768;

a 2,3-dihydro-benzofuran-7-carboxamide compound,  
preferably ADR 932, Prucalopride (=R 093877), and SK-951;



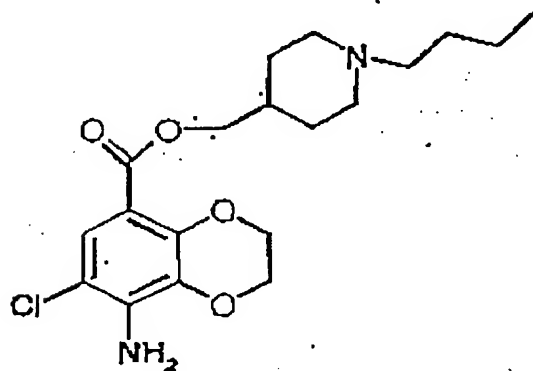
benzofuranes and benzothiophenes,



35

the benzodioxan

5

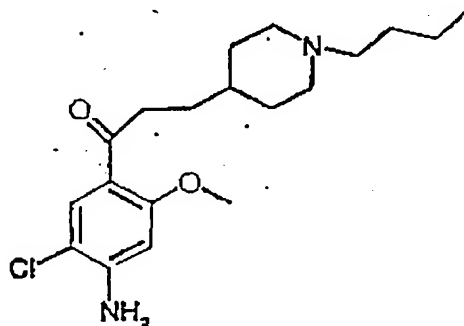


SB 204070

10

the benzoic acid antagonist RS 23597 (an ester)  
transformed to an agonist by conversion to a ketone

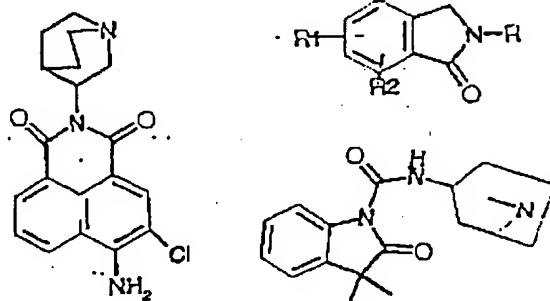
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20

e.g. preferably RS 67333 and RS 17017;  
naphtalimides, preferably RS 56532;

25



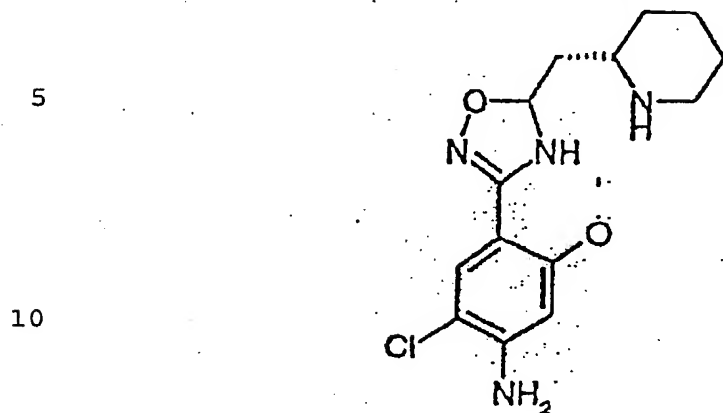
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benzindolones;

35

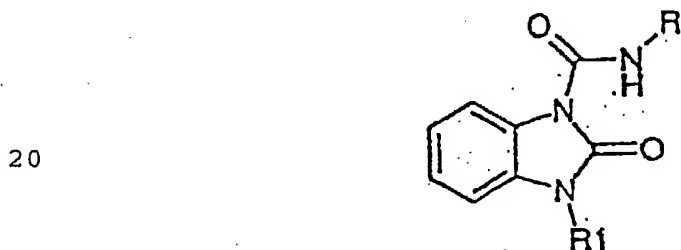
36

compounds in which the amide function has been re-  
placed with an oxadiazol ring;



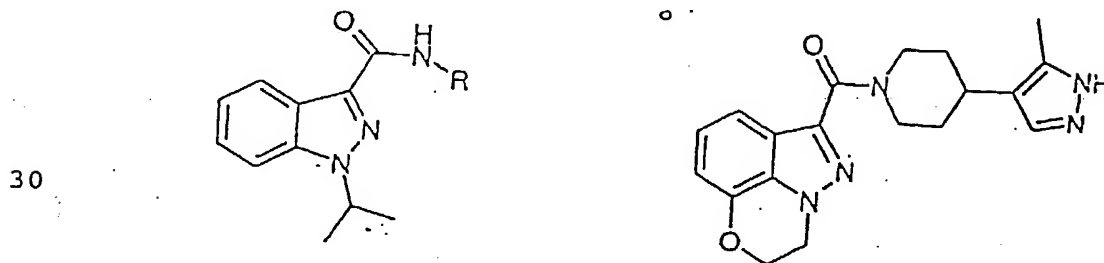
preferably YM-53389;

15 benzimidazolone-1-carboxamides



preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

25 the carboamides



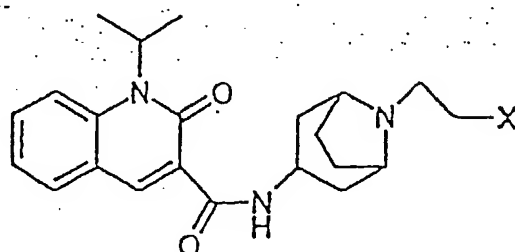
indols, preferably 5-methoxytryptamine, 2-methyl-  
35 serotonin, and 5-hydroxy-N,N-di-methyltryptamine;

23-10-2001

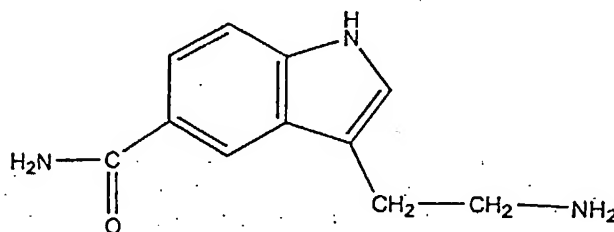
37

compounds quaternized on the nitrogen in the side chain:

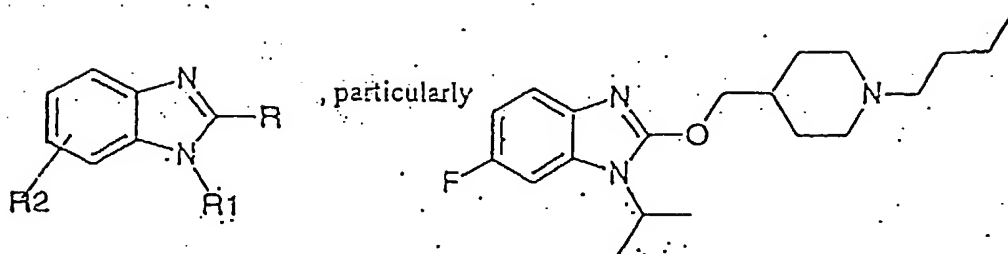
benzokinolinones



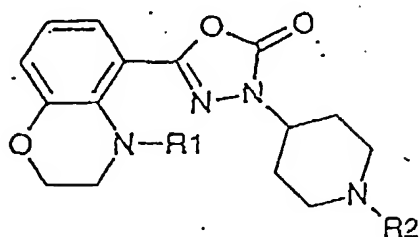
5-carboxamidotryptamine (5-CT), with the structural formula:



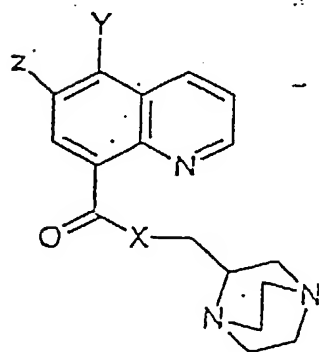
- 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808,  $\alpha$ -methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5-azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,



2-piperidinmethylethers  
of bensimidazol

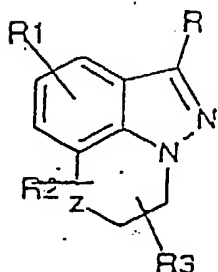
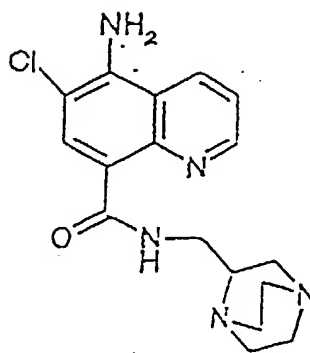


oxadiazalon based  
substance

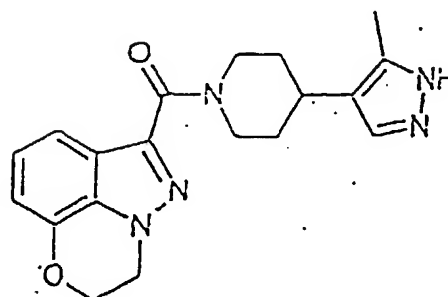


kinolines

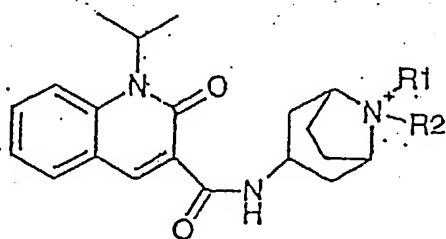
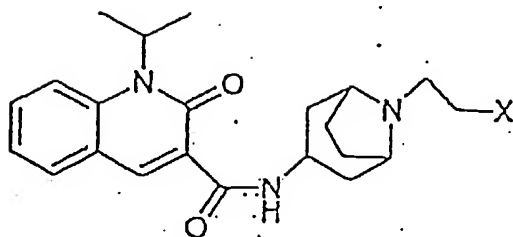
, particularly



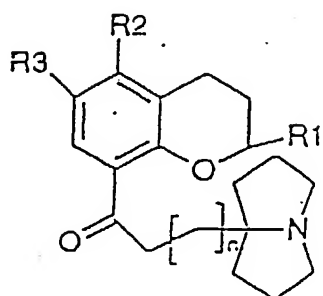
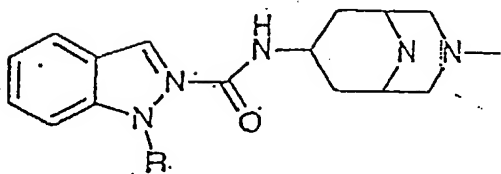
, particularly



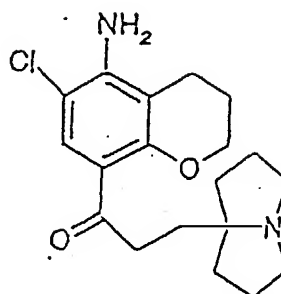
39



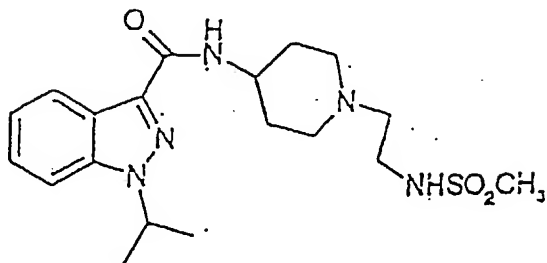
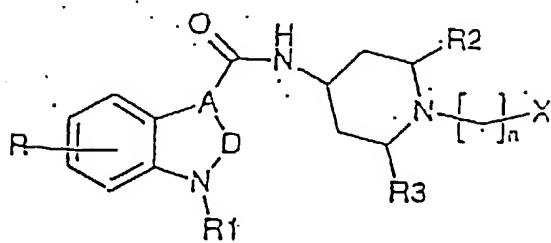
Q



, particularly



benzopyrrolones



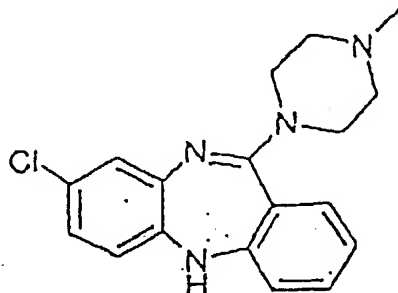
and derivatives and pharmaceutically acceptable salts thereof.

2. Use according to claim 1, wherein said compound is VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine, 5  
Zacopride, RS56532, Mosapride, BRL 24924, or SC 53116.

3. Use according to any one of the previous claims, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

4. A method for treatment of disorders involving  
10 bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according  
15 to any one of claims 1 and 2.

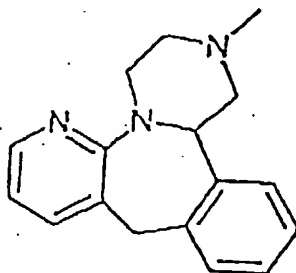
5. Use of one or more compounds having antagonist activity to a 5-HT<sub>3</sub> receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT<sub>3</sub> receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of  
20 disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have  
25 the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 5-HT<sub>3</sub> receptor antagonists



41

benzazepines, preferably mirtazapine

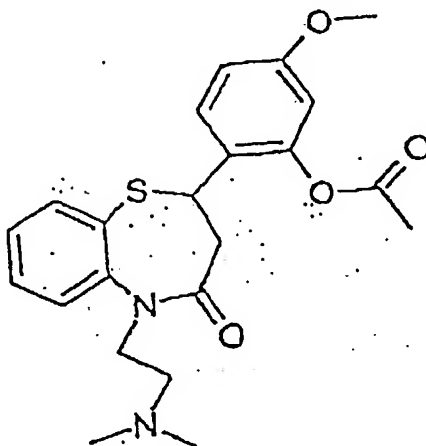
5



10

benztiazepines, preferably diltiazem

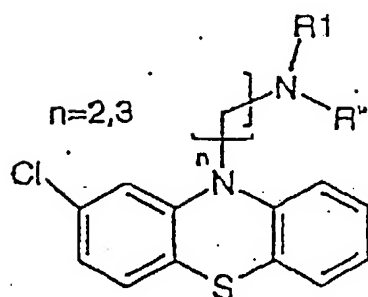
15



20

and fentiazines

25

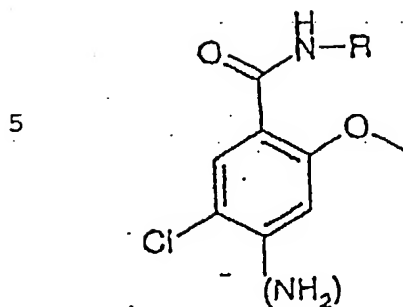


30

preferably perphenazine, stemetil;

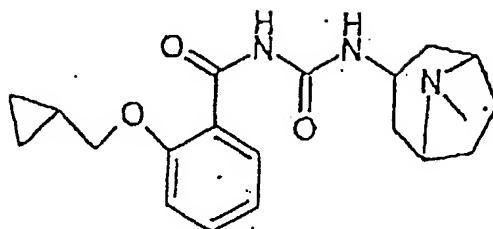
compounds also having 5-HT<sub>4</sub> receptor agonist activity, preferably benzamides

35



(cisapride, zacopride,  
mosapride, pancropride,  
BRL 24924, BMY 33462)

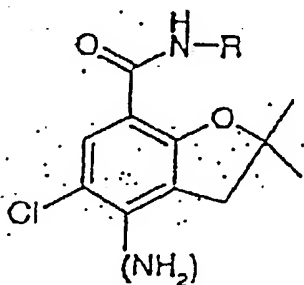
10 and



WAY 100289

2,3-dihydro-benzofuran-7-carboxamides

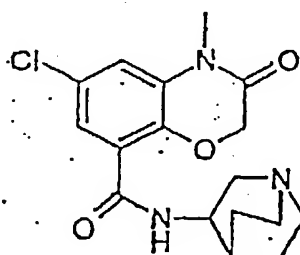
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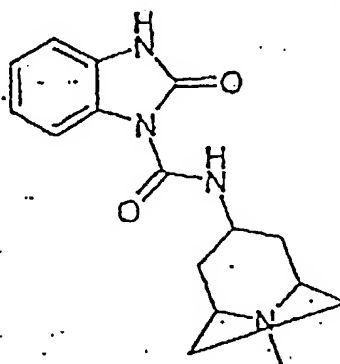
(preferably zatosetron=LY 277359, ADR 851);  
1,4-benzoxazin-8-carboxamides

30



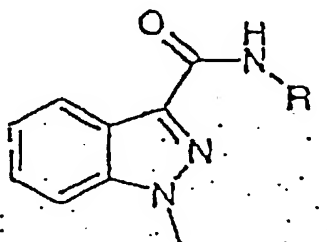
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preferably azasetron (=Y25130);  
benzimidazolones



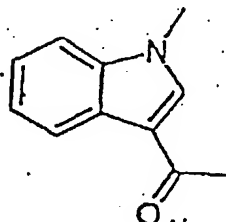
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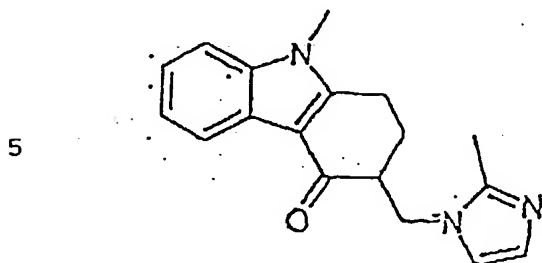
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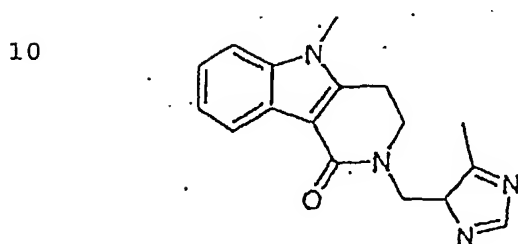


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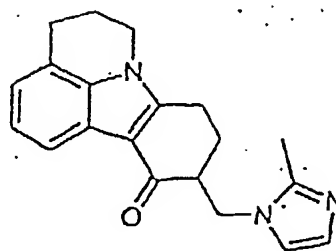
in different forms, such as



ondansetron

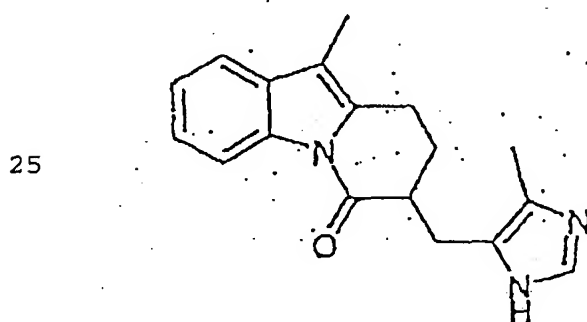


alosetron



cilansetron

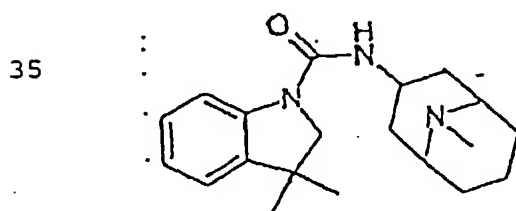
substances the structure of which has been inverted and  
the carbonyl group has been placed on the indoline nitro-  
gen



FK 1052

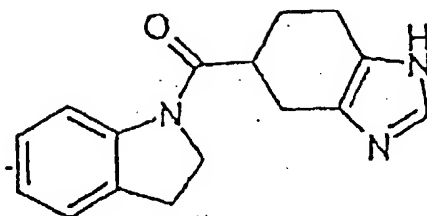
30

also being an antagonist against both 5-HT<sub>3</sub> and 5-HT<sub>4</sub> re-  
ceptors,



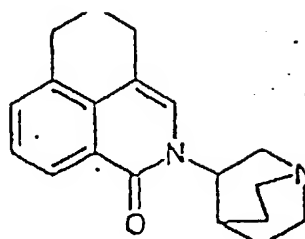
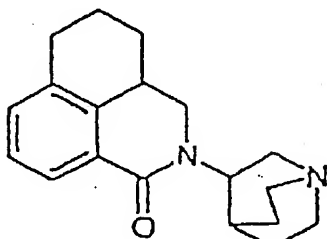
BRL 46470 A

5



YM 114

10 isoquinoline-1-ones

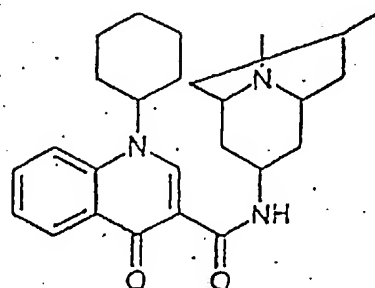
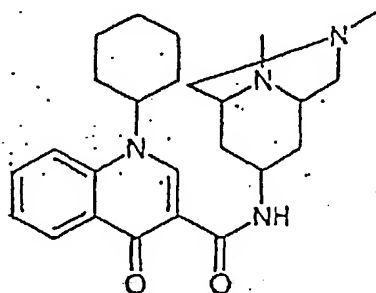


palonosetron (=RS 25259-197)

RS 42358-197

20 and the quinoline-3-carboxamides

25



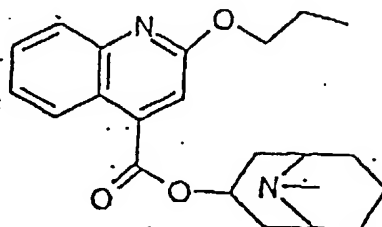
30

WAY-SEC 579

Mirisetron (=WAY 100579),

quinoline-4-carboxylates

35

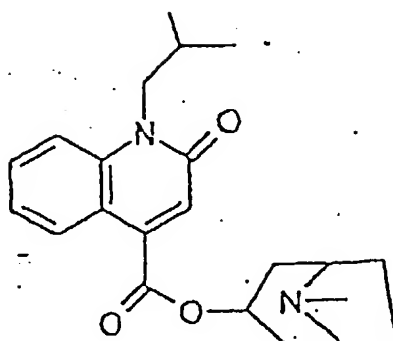


46

preferably KF 17643

5

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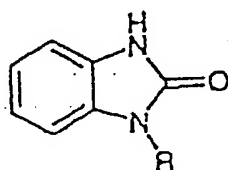


preferably KF 18259;

15

benzimidazolones

20

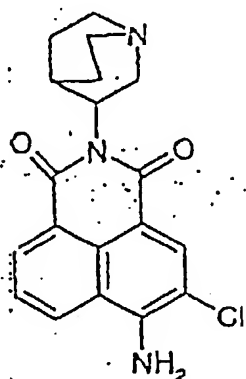


preferably itasetron (DAU6215),

and the naphthimides

25

30



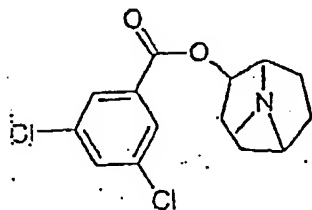
RS 56532

35 preferably RS 56532;

47

MDL 72222, which also is a specific 5-HT<sub>2</sub> antago-  
nist;

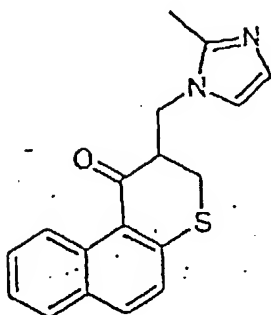
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; and

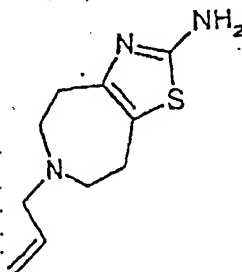
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GK 128

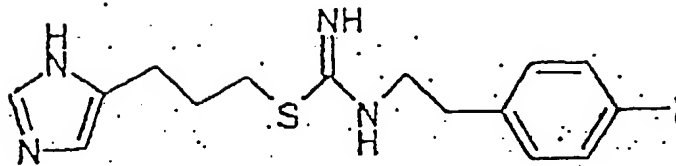
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Talipexole

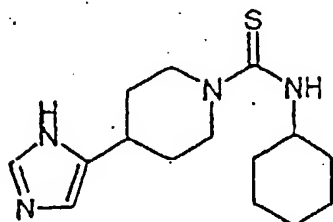
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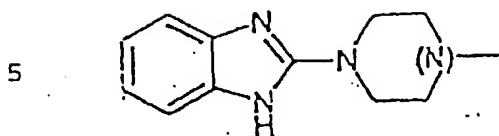


iodophenpropit

35



thioperamide, and



2-piperidin- and 2-piperazin-  
benzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-  
10 ((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204,  
15 Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922,  
20 KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPPE, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-methylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide,  
25 Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8,  
30 trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ  
35 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect,

and derivatives and pharmaceutically acceptable salts thereof.

6. Use according to claim 5, wherein said compound is Tropanyl 3,5-dimethylbenzoate, MDL 72222, SDZ 216-525,  
5 ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron, or Cilansetron.

7. Use according to any one of claims 5 and 6, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

10 8. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a  
15 therapeutically effective amount of a compound according to any one of claims 5 and 6.

9. Use of a composition comprising a combination of at least one compound with agonist activity to the 5-HT<sub>4</sub> receptor, and at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor, for the manufacture of a  
20 medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive  
25 pulmonary disease, preferably asthma and disorders related thereto.

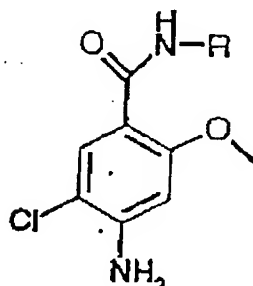
10. Use according to claim 9, wherein said composition has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and  
30 most preferably at least 90%, and wherein said combination is chosen from the following groups of

a) 5-HT<sub>4</sub> receptor agonists:

benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopra

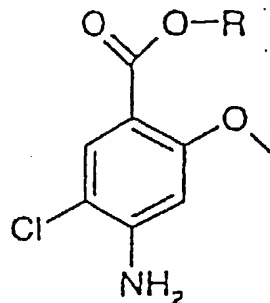
35

mide, with the structural formula:



having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

benzoic acid esters:



30 preferably ML 10302, RS 57639, and SR 59768;  
a 2,3-dihydro-bensofuran-7-carboxamide compound,

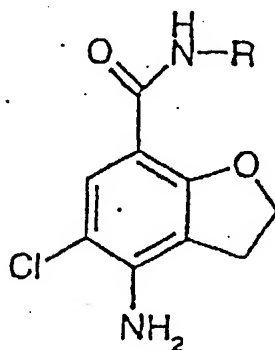
35

51

preferably ADR 932, Prucalopride (=R 093877), and SK-951;

5

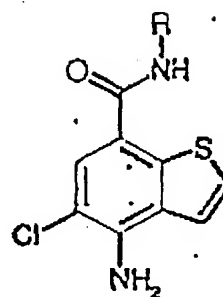
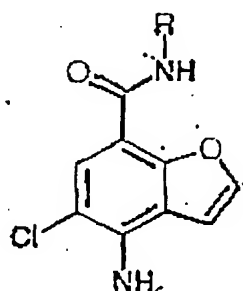
10



benzofuranes and benzothiophenes,

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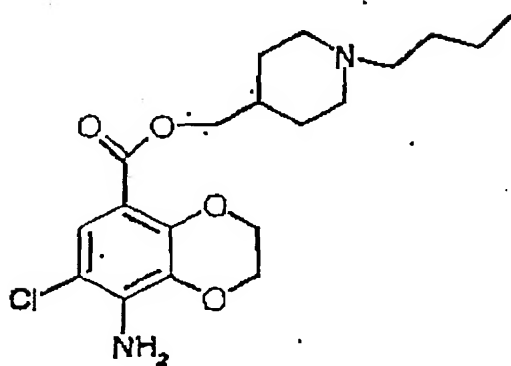


the benzodioxan

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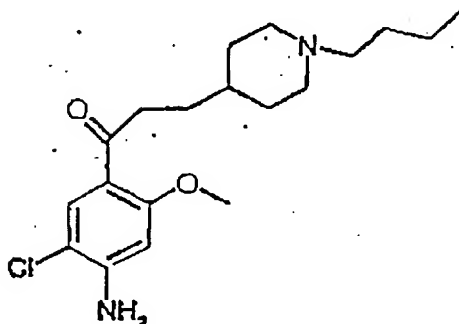
SB 204070

52

the benzoic acid antagonist RS 23597 (an ester)  
transformed to an agonist by conversion to a ketone

5

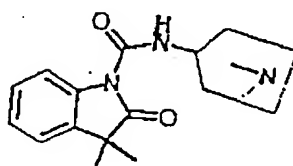
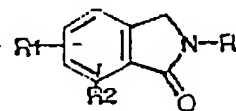
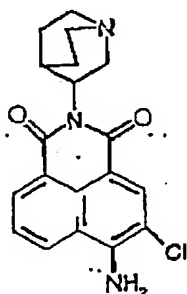
10



e.g. preferably RS 67333 and RS 17017;  
naphthalimides, preferably RS 56532;

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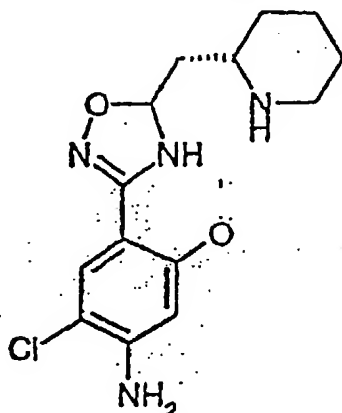
benzindolones;

25

compounds in which the amide function has been re-  
placed with an oxadiazol ring;

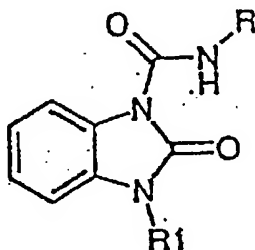
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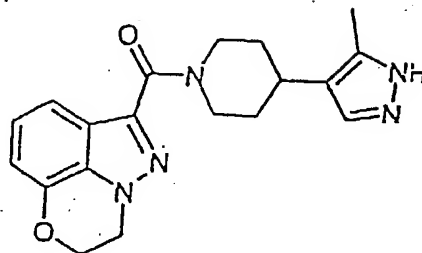
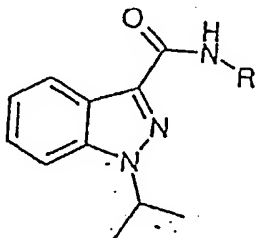


53

preferably YM-53389;  
benzimidazolone-1-carboxamides



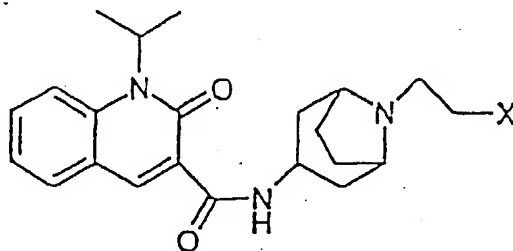
preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;  
the carboamides



indols, preferably 5-methoxytryptamine, 2-methyl-  
serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side  
chain:

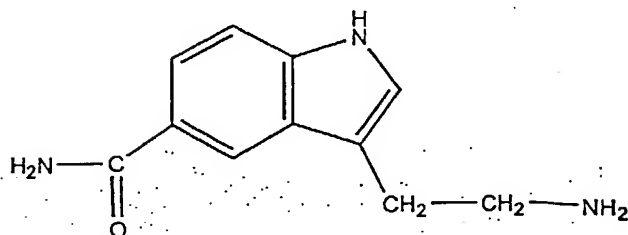
benzokinolinones



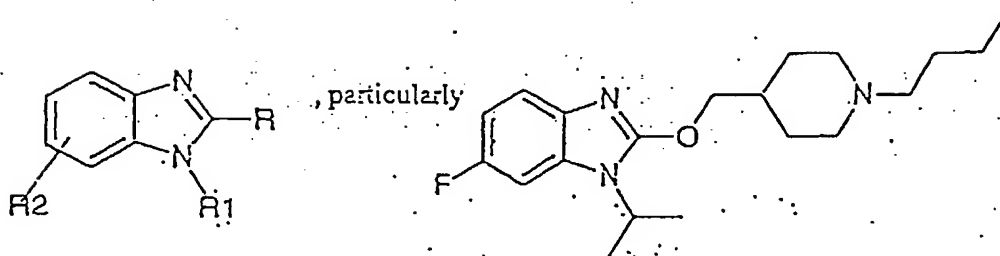
5-carboxamidotryptamine (5-CT), with the structural  
formula:

23-10-2001

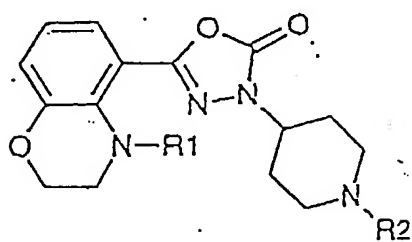
54



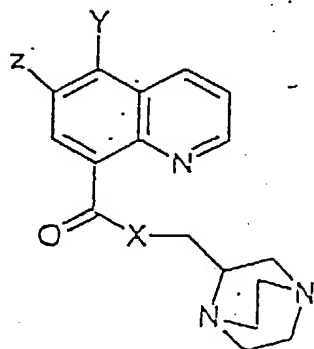
- 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808,  $\alpha$ -methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxy-methyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,



2-piperidinmethylethers  
of bensimidazol

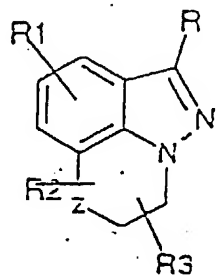
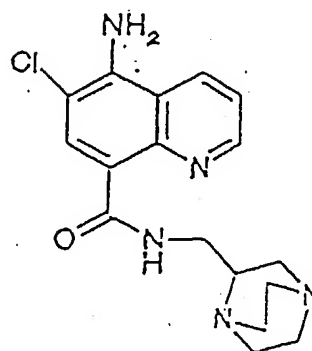


oxadiazolon based  
substance

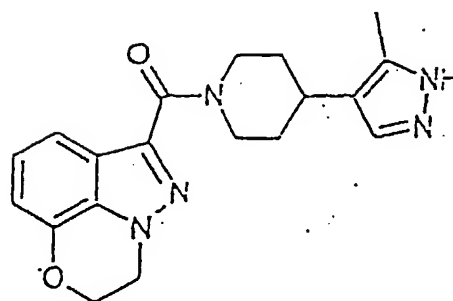


kinolines

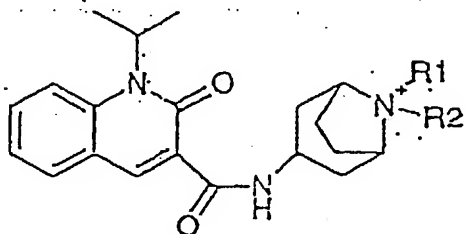
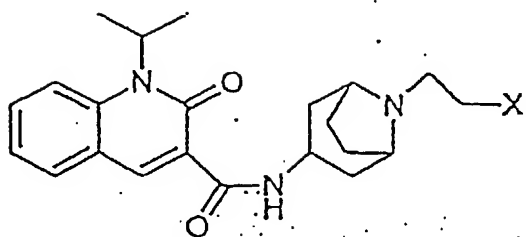
, particularly



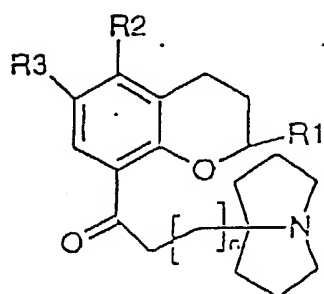
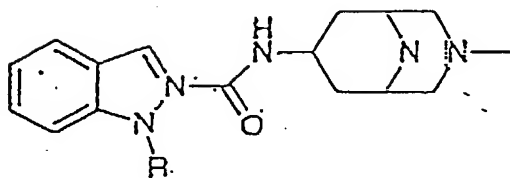
, particularly



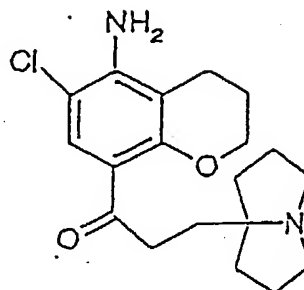
56



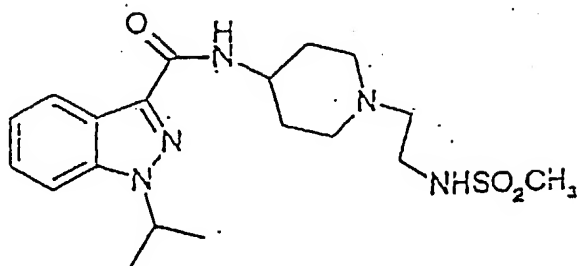
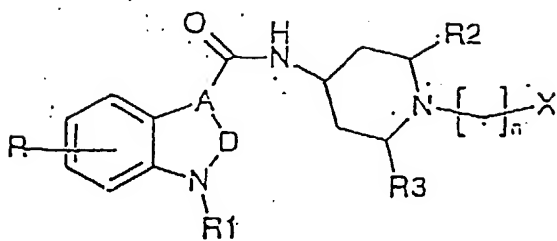
Q



, particularly

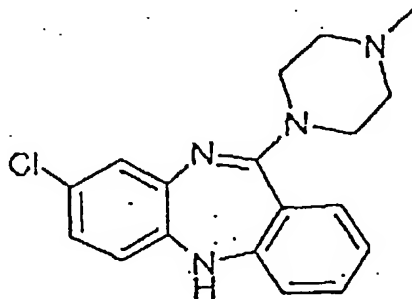


benzopyranes

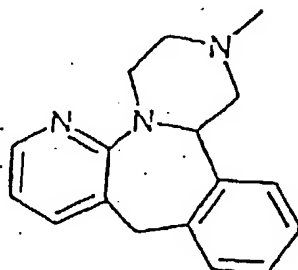


57

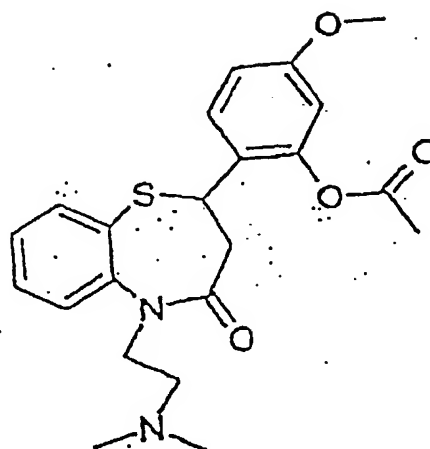
b) 5-HT<sub>3</sub> receptor antagonists:



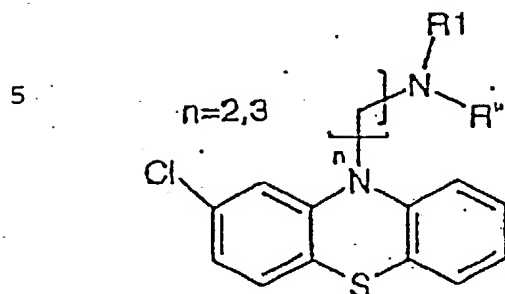
benzazepines, preferably mirtazapine



benztiazepines, preferably diltiazem



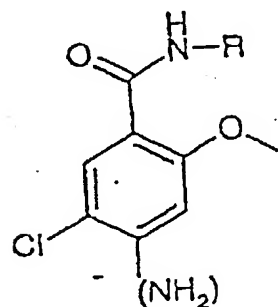
and fentiazines



preferably perphenazine, stemetil;

compounds also having 5-HT<sub>4</sub> receptor agonist activity, preferably benzamides

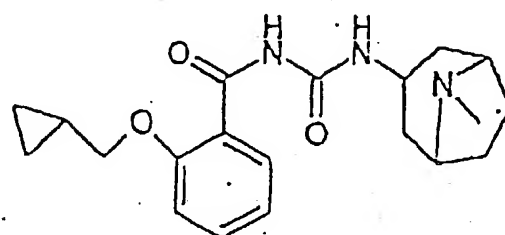
15



(cisapride, zacopride,  
mosapride, pancopride,  
BRL 24924, BMY 33462)

and

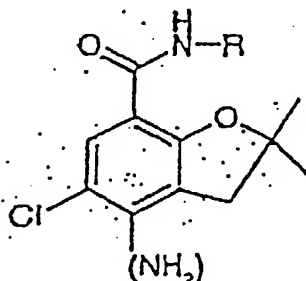
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WAY 100289

2,3-dihydro-benzofuran-7-carboxamides

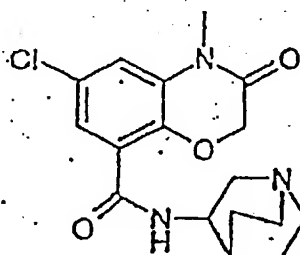
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59

(preferably zatosetron=LY 277359, ADR 851);  
1,4-benoxazin-8-carboxamides

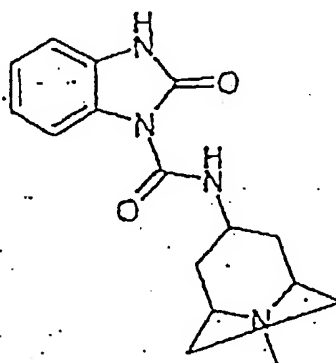
5



10

preferably azasetron (=Y25130);  
benzimidazolones

15



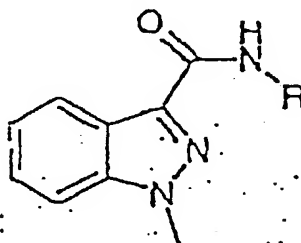
20

preferably itasetron (=DAU 6215);

25

indazol-3-carboxamides

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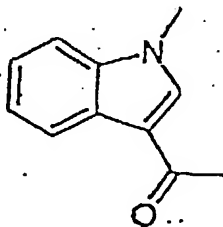
preferably N 3389, LY 278584, DAT 582;

35

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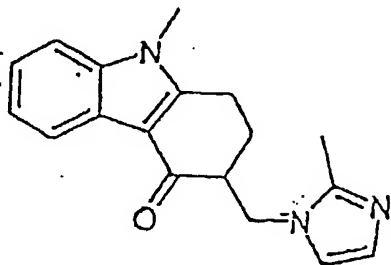
wherein the latter group reminds most of the specific 5-HT<sub>3</sub> antagonists, which contains the group

5



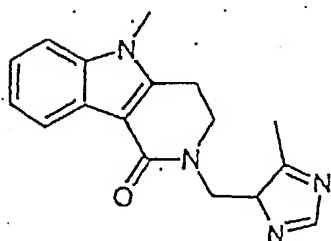
10 in different forms, such as

15

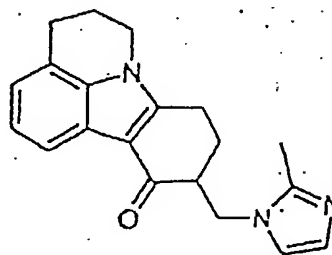


ondansetron

20



25 alosetron

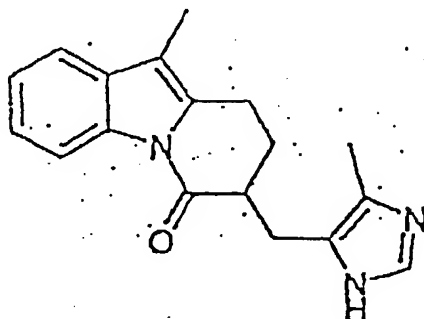


cilansetron

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substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen

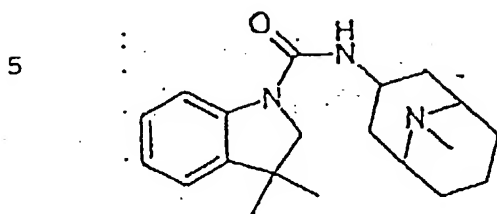
30



FK 1052

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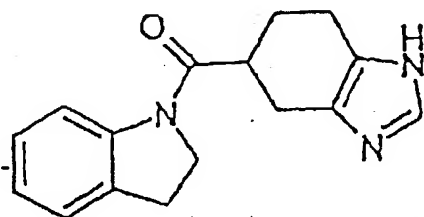
also being an antagonist against both 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors,



BRL 46470 A

bisindoles

10

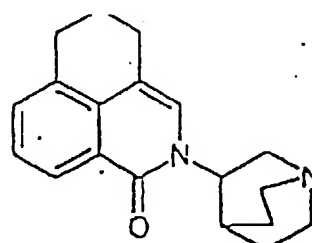
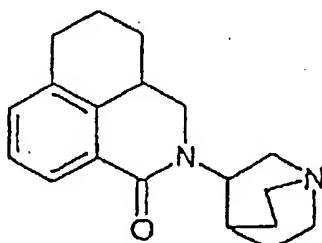


YM 114

15

isoquinoline-1-ones

20



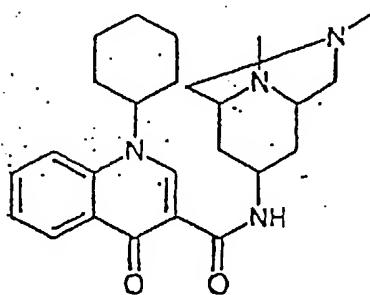
25

palonosetron (=RS 25259-197)

RS 42358-197

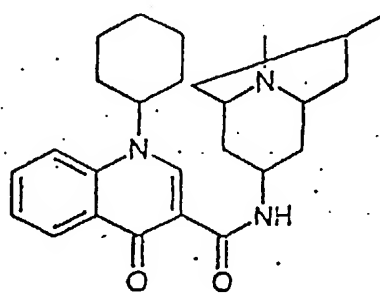
and the quinoline-3-carboxamides

30



35

WAY-SEC 579

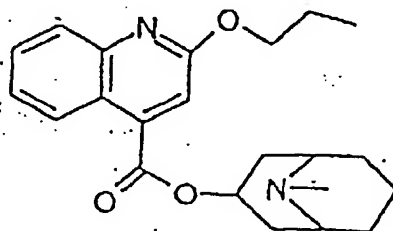


Mirisetron (=WAY 100579),

62

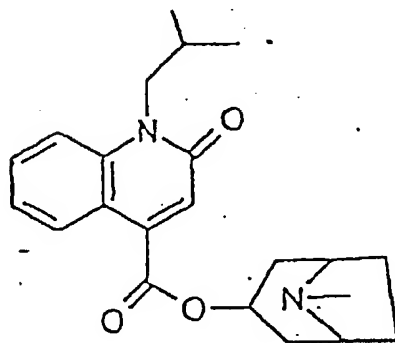
quinoline-4-carboxylates

5



10 preferably KF 17643

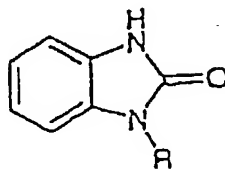
15



20 preferably KF 18259;

benzimidazolones

25



preferably itasetron (DAU6215),

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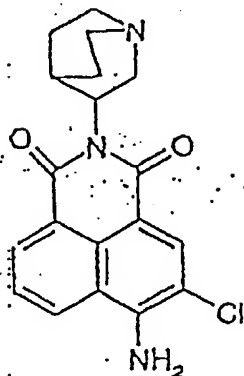
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and the naphtimides

5

RS 56532

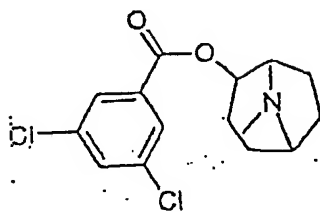
10



preferably RS 56532;

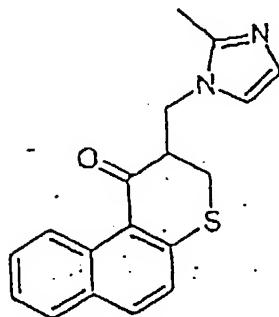
MDL 72222, which also is a specific 5-HT<sub>2</sub> antago-  
nist;

20



; and

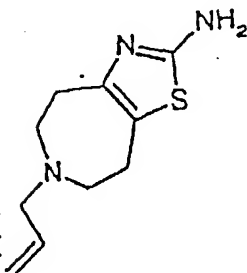
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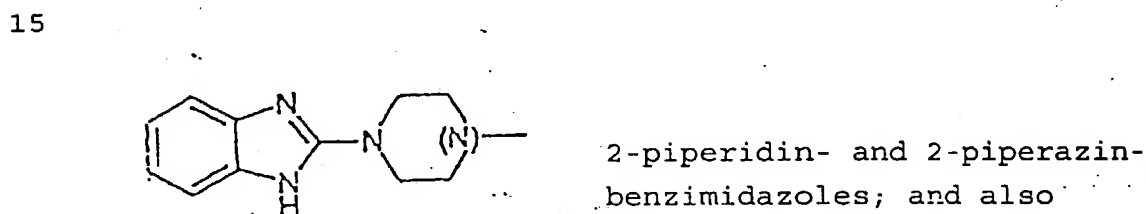
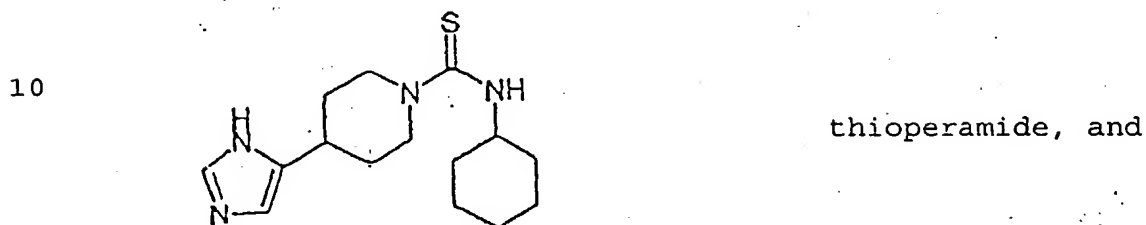
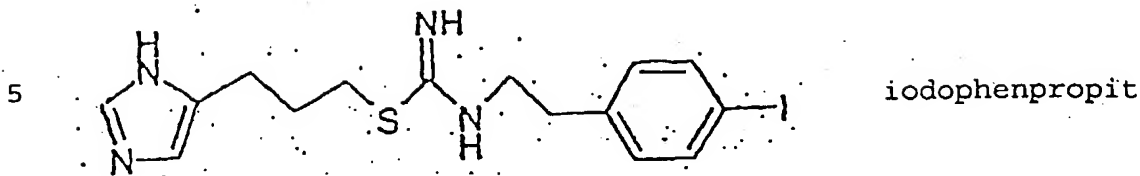
GK 128

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35



Talipexole



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(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat

25

(=MDL 73147 EF), Fluphenazone, Galdanasetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCP, MDL

30

72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-methylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide,

35

Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, 5 SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, 10 Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect, and derivatives and pharmaceutically acceptable salts 15 thereof.

11. Use according to claim 10, wherein the composition comprises the following combinations of a 5-HT<sub>4</sub> receptor agonist and a 5-HT<sub>3</sub> receptor antagonist: VB20B7 and Tropanyl 3,5-dimethylbenzoate, VB20B7 and MDL 72222, 20 RS67333 and Tropanyl 3,5-dimethylbenzoate, RS76333 and MDL 72222, VB20B7 and ICI 169369, RS67333 and ICI 169369, Zacopride and Tropanyl 3,5-dimethylbenzoate, Zacopride and MDL 72222, RS56532 and Tropanyl 3,5 dimethylbenzoate, RS56532 and MDL 72222, Itasetron and Tropanyl 3,5- 25 dimethylbenzoate, Itasetron and MDL 72222, VB20B7 and SDZ 216-525, and RS67333 and SDZ 216-525.

12. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic 30 bronchitis, and chronic obstructive pulmonary disease, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a composition according to any one of claims 10 and 11.

13. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic 35 bronchitis, and chronic obstructive pulmonary disease,

wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a 5-HT<sub>4</sub> receptor agonist according to any one of claims 1 and 2 and a 5-HT<sub>3</sub> receptor antagonist according to any one of claims 5 and 6, either simultaneously or sequentially.